antibodies, and to screen drugs, and that while these utilities are credible, they are allegedly neither specific nor substantial (pages 2-5 of the November 19, 2001 Office Action). Applicants respectfully traverse this rejection.

Applicants maintain that the utilities the Patent Office acknowledges to be credible in the Office Action are also specific and substantial. In particular, in view of: a) the strong association between the genomic region encoding the present protein and schizophrenia; b) the fact that the present protein is expressed mainly in the brain; c) the fact that the protein is a novel member of a family of proteins frequently implicated in neuropsychiatric disorders; and d) G713 being a candidate gene for neuropsychiatric disorders, on the basis of both structure and function (see *infra*); Applicants submit that the present protein has specific and substantial utility in the identification of individuals at risk for the development of neurodegenerative disorders or the treatment and diagnosis of neuropsychiatric disorders such as schizophrenia.

Substantial utility

The Office Action alleges that the cited utilities of the protein encompassed by the present claims that are provided in the specification are not substantial. Applicants respectfully traverse.

In particular, the Office Action states that evidence of the association of all glutamine repeat proteins with any disease state might be sufficient to provide a substantial utility. Applicants respectfully submit that this is not the standard for the establishment of the utility of an invention. The evidentiary standard for application in this matter is "preponderance of the evidence". Thus, the issue is more properly framed as, "Is it more likely than unlikely that proteins containing polyglutamine repeats are associated with neurodegenerative diseases?" To this end, the Office Action indicates that:

"...many [genes] have glutamine repeats. A search of STN revealed that 14,560 sequences in the database which had a 3 repeat sequence of CAGCAGCAG, of which 6,723 were associated with human sequences" (page 4, November 19, 2001 Office Action).

Applicants respectfully submit that this analysis is irrelevant to the question at hand. As recognized by the Patent Office, previously presented in arguments by Applicants' counsel, and presented herein, proteins containing glutamine repeats, and expansions of such repeats, are associated with at least twelve (12) diseases, including neurodegenerative diseases. Thus, Applicants respectfully submit that those skilled in the art are well aware of the relationship between glutamine repeats and neurological disorders. Furthermore, Applicants respectfully submit that, on the basis of its expression in brain and its CAG (glutamine) repeat (among other hallmarks of repeats known to undergo expansion in disease states), a person of ordinary skill in the art would "consider [G713] a candidate gene for neuropsychiatric disorder on the basis of both structure and function" [paragraph bridging pages 119-20; Margolis *et al.* [1997] *Human Genetics* 100:114-122; Exhibit A]. Additionally, given the occurrence of sequential repeats of four glutamines, nine glutamines, and six glutamines within the G713 protein, Applicants respectfully submit that a person of ordinary skill in the art would perceive the use, by the Patent Office, of "a 3 repeat sequence of CAGCAGCAG [$(CAG)_3$]" rather than a 9-19 repeat sequence of $(CAG)_{9\text{-}19}$ to be inappropriate for assessing the significance of the glutamine repeat within G713.

It is further respectfully submitted that an absolute number of 6,723 hits for proteins containing a three repeat glutamine sequence is meaningless. In the context of this invention, it is the number and relationship of glutamine repeats with neurodegenerative disorders that are of

significance. Applicants respectfully submit that a more meaningful number is obtained from the paper by Margolis *et al.* (Exhibit A), wherein it was found that about 20 distinct cDNA clones were isolated from screening 200,000 or more plaques of human brain cDNA libraries with $(CAG)_{15}$. This corresponds to a representation of glutamine repeat within brain cDNA on the order of about 0.01%, a value inconsistent with the Patent Office's assertion that "*many* [genes] have glutamine repeats" [emphasis added; page 4, November 19, 2001 Office Action]. Indeed, the skilled artisan would reasonably expect that genes and proteins containing high numbers of glutamine repeats are associated with neurodegenerative disorders on the basis of structure and function in neurological tissue (Margolis *et al.*, Exhibit A, paragraph bridging pages 119-120). Thus, Applicants respectfully submit that a person of ordinary skill in the art would find reasonable Applicants' conclusion that G713 is suitable for screening as a marker for neuropsychiatric disorders on the basis of both structure and function.

Applicants also respectfully point out that the M.P.E.P. at § 2107.02 states, with reference to *In re Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Applicants respectfully submit that: 1) in view of the strong association between the genomic region encoding the present protein and schizophrenia; 2) in view of the fact that the present protein is expressed mainly in the brain; 3) in view of the fact that the protein is a novel member of a family of proteins frequently implicated in neuropsychiatric disorders; and 4) in view of G713 being a candidate gene for neuropsychiatric disorder on the basis of both structure and function, that there is

a correlation or association of the present protein with predisposition to the onset of neuropsychiatric disorders such as schizophrenia. As stated in the M.P.E.P. at § 2107.01:

> *An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition* [emphasis added] would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring.

As one of the cited utilities of the protein encompassed by the present claims that are provided in the specification is to detect the protein (see *supra*), Applicants respectfully submit that the utilities, of the protein encompassed by the present claims, provided in the specification are substantial.

Specific utility

The Office Action also alleges that cited utilities, of the protein encompassed by the present claims, that are provided in the specification are "not specific because Perutz ([1996] *Current Opinion Structural Biology* 6:848-58) ... has identified many different proteins with glutamine repeats, all of which are associated with different diseases and Kashima has identified at least one protein not disease associated with glutamine repeats" (page 4, November 19, 2001 Office Action).

Applicants respectfully dispute the Patent Office's representation of the Perutz paper. In the first sentence, Perutz states: "*Several* [emphasis added] dominantly inherited, late onset, *neurodegenerative diseases* [emphasis added] are due to expansion of CAG repeats, leading to expansion of glutamine repeats in the affected proteins." Perutz then proceeds to discuss only *seven* neurodegenerative diseases. Furthermore, as indicated in Margolis *et al.*, twelve (12) diseases, most with neurotrophic features, arise from trinucleotide repeat expansion mutations (see Abstract and Introduction).

Applicants further respectfully traverse the relevance of the Kashima paper. The observation by Kashima *et al.* that "the consecutive glutamine repeats do not play a role in the biological and immunological activities of MIL-2" (page 4, November 19, 2001 Office Action) is irrelevant to examination of the present application. Applicants further respectfully submit that as MIL-2 is not expressed in brain, MIL-2 is *a priori* irrelevant to any discussion of the role of CAG repeats, and their expansion, in neuropsychiatric disorders such as schizophrenia. Furthermore, Kashima *et al.*, and the teachings therein, are directed to the structure and function of murine interleukin 2 (MIL-2) and contain no teachings with respect to neurodegenerative disorders. Thus, it is unclear what, if any, nexus or evidentiary value the reference has to the assessment of the role of glutamine repeats in neurodegenerative disorders. Furthermore, as the Office Action acknowledges, glutamine repeats, and their expansion, are art recognized to be associated with a variety of neurodegenerative disorders, such as schizophrenia. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 112:

In the Office Action dated November 19, 2001, the Patent Office rejected claims 58, 62, and 73-75 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. Specifically, the Office Action alleges that the cited utilities, of the protein encompassed by the present claims, that are provided in the specification allegedly are not specific. Applicants respectfully traverse this rejection.

Nature of Invention

Claims are drawn to a G713 protein and methods of detection of this protein or gene product. The Office Action alleges that "the nature of this invention is a ... protein, with no other associated information" [page 5-6, November 19, 2001 Office Action].

Applicants respectfully traverse this representation of the invention in view of: 1) the strong association between the genomic region encoding the present protein and schizophrenia; 2) the fact that the present protein is expressed mainly in the brain; 3) the fact that the protein is a novel member of a family of proteins frequently implicated in neuropsychiatric disorders; and 4) the fact that G713 is a candidate gene for neuropsychiatric disorder on the basis of both structure and function (see *supra* and *infra*).

Breadth of the Claims

As the Patent Office acknowledges, "claims ... are drawn to a G713 protein and methods of detection of this protein or gene product" [page 5, November 19, 2001 Office Action].

Amount of Guidance in the Specification

The Office Action alleges that the utilities of the protein encompassed by the present claims that are provided in the specification are "not found to be substantial nor specific and, consequently, the specification provides NO guidance regarding how to use this protein" [page 6, November 19, 2001 Office Action]. Applicants respectfully disagree. As indicated *supra,* the subject invention provides credible, substantial, and specific uses of the presently claimed invention. Applicants submit that the argument of a consequential lack of "guidance regarding how to use this protein", arising from the allegation that the invention lacks specific and substantial utility, is improper and respectfully request reconsideration and withdrawal of this point of rejection.

Working Examples

The Office Action also alleges that "the absence of working examples in the specification" [page 8, November 19, 2001 Office Action] is a valid basis for a conclusion that "undue experimentation would be required to use this invention as claimed" [page 8, November 19, 2001 Office Action]. Applicants respectfully traverse this point of rejection and submit that a person of ordinary skill in the art would know how to use the present invention in an "assay for detection or diagnosis" [page 6, November 19, 2001 Office Action]. In support of Applicants' position, it is noted that just one type of assay encompassed by the method of claim 73, namely enzyme linked immunosorbent assays, is associated with at least 3307 references in PubMed [Exhibit B].

Amount of Guidance in Prior Art

The Office Action also argues that "the prior art provides no guidance with regard to the particular function of the G713 protein and does not even provide support or guidance for glutamine repeat containing proteins having a particular use or association" [page 6, November 19, 2001 Office Action]. It is respectfully submitted that this allegation is without basis in view of the art-recognized association of glutamine repeats with neurodegenerative diseases (see, for example, Margolis *et al.*).

The Patent Office also reiterates an argument based on the Kashima paper. As indicated supra, the relevance and evidentiary value of the Kashima paper to the instant invention is unclear. The reference concerns the role of glutamine repeats in the biological function of a murine cytokine and is devoid of any teachings related to glutamine repeats and their association with neurodegenerative disorders. Applicants further reiterate that in the context of the present invention, whether glutamine repeats play a role in the normal function of a given protein is irrelevant; as

explicitly acknowledged elsewhere by the Patent Office, high numbers of glutamine repeats, and their expansion, are hallmarks of neurodegenerative disorders and the proteins associated therewith.

Skill in the Art

The Patent Office believes that "the skill in the art would be considered high" [page 7, November 19, 2001 Office Action]. Applicants concur.

Predictability of the Art

The Patent Office cites a review article by Wright *et al.* ([2001] *Schizophrenia Research* 47:1-12) to support his assertion of the "unpredictability in this linkage of schizophrenia with chromosomal locations" (page 7, November 19, 2001 Office Action). Applicants respectfully dispute the Patent Office's representation of linkage studies of schizophrenia as unpredictable. Genetic analysis of schizophrenia and other diseases believed to have a number of susceptibility loci are complicated but *not invalidated* by issues of population stratification and statistical power. These considerations are well appreciated by persons of ordinary skill in the art and are discussed, for example, in Weinberger *et al.* ([2001] *Biological Psychiatry* 50:825-44; Exhibit C).

The issue of population stratification is well known to Applicants as evidenced by the analysis presented in Example 2(g) of the specification (pages 164, 167, and 174). Example 2(g) presents the results of an association study between schizophrenia and the biallelic markers of the invention. In that study, it was found that "the relative difference in Mean normalized LD for BAC B5 is significantly higher when the comparison was made between *familial cases* and controls than when the comparison was made between the *whole cases* and the controls [emphasis added]" (page 167).

That the issue of population stratification is well known to persons of ordinary skill in the art is evidenced by the study presented in the paper by Brant *et al.* ([2000] *Gastroenterology* 119:1483-90; Exhibit D) dealing with genetic analysis of the analogously complex Crohn's disease (CD) and as discussed therein with reference to other studies. In the paper by Brant *et al.*, it was found that: "Pedigrees with CD diagnosed at an earlier age have greater linkage evidence for IBD1. This effect is greatly magnified when the *individuals with younger onset also have relatively more severe disease...*" (page 1488) [emphasis added].

The issue of statistical power is well known to Applicants as evidenced by patents (for example, U.S. Patent No. 6,291,182; Exhibit E) and proprietary software directed to the statistical analysis involved in determining whether a genomic region is associated with a detectable trait such as schizophrenia.

Applicants further dispute the Patent Office's assertion of "unpredictability in this linking of schizophrenia with chromosomal locations" (page 7, November 19, 2001 Office Action) in view of Applicants' success in further associating schizophrenia with gene g35030 (WO 01/40493; Exhibit F) and in view of others' success in identifying an association of catechol-o-methyl transferase (COMT) gene with schizophrenia [Weinberger *et al.* [2001] *Biological Psychiatry* 50:825-44; Exhibit C].

In view of the foregoing evidence, Applicants respectfully submit that the Patent Office allegation regarding the "unpredictability in this linkage of schizophrenia with chromosomal locations" (page 7, November 19, 2001 Office Action) is improper. Reconsideration and withdrawal of the rejection is respectfully requested.

Quantity of Experimentation

The Office Action alleges that "an immense amount of experimentation would be required in order to define whether this protein is associated with any particular disease state" and concludes that "undue experimentation would be required to use this invention as claimed" (page 7, November 19, 2001 Office Action). Applicants respectfully dispute this representation of the invention in view of the strong association between the genomic region encoding the present protein and schizophrenia, in view of the fact that the present protein is expressed mainly in the brain, in view of the fact that the protein is a novel member of a family of proteins frequently implicated in neuropsychiatric disorders, and in view of G713 structure and function that is suggestive of roles in neurodegenerative disorders. It is further submitted that that there is a correlation of the present protein to a predisposition to the onset of neuropsychiatric disorders such as schizophrenia (see *supra*). Applicants respectfully submit that the Patent Office has failed to establish a *prima facie* case regarding a lack of enablement and respectfully request reconsideration and withdrawal of the rejection.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: Saliwanchik, Lloyd & Saliwanchik
A Professional Association
2421 NW 41st Street, Suite A-1
Gainesville, FL 32606-6669

FCE/jaj

Attachments:
Exhibit A: Margolis *et al.* [1997] *Human Genetics* 100:114-122
Exhibit B: List of 3307 references in PubMed
Exhibit C: Weinberger *et al.* [2001] *Biological Psychiatry* 50:825-44
Exhibit D: Brant *et al.* [2000] *Gastroenterology* 119:1483-90
Exhibit E: U.S. Patent No. 6,291,182
Exhibit F: Patent No. WO 01/40493